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MORRISON & FOERSTER LLP
3811 VALLEY CENTRE DRIVE
SUITE 500
SAN DIEGO, CA 92130-2332

EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,224	SHORT ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-55,88-96,101,103,106,107,110-112 and 115-138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-55, 88-96, 101, 103, 106-107, 110-112, 115-138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 42-55, 88-96, 101, 103, 106-107, 110-112, 115-133, and newly added claims 134-138 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are either newly applied, as necessitated by amendment, or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The rejection of claims 90-92 under 35 USC 112/2nd paragraph made at section 10 of the previous office action is moot in view of the amendments to the claims.

Response to Arguments regarding Priority

4. The response traverses the previous office action's assessment of priority for the instantly pending claims. At page 18, the response asserts that the claimed subject matter need not be described in haec verba in the parent specification to satisfy the description requirement. The response asserts that support for the claims can be found in the instant specification. This argument is not found persuasive because the previous office action did not reject the instantly pending claims under the written description portion of 35 USC 112, first paragraph. The response further asserts at pages 18-19 that the parent specification, at column 8, lines 24 to 38 in

USPN 5,789,228 provides support by describing the invention as encompassing nucleic acids having at least 70% identity to exemplary nucleic acids of the invention, and that as such, one of skill in the art would recognize from the disclosure that applicant's invented the subject matter of the pending claims. The response further asserts that column 8, lines 39 to 47 and 48-54 provide support for at least 30 consecutive bases and that such supports the claimed fragments. This argument has been thoroughly reviewed but was found unpersuasive. It is noted that the instant application is a CIP application of the earlier filed parent applications. The disclosure of the parent specification ('228) represents a general disclosure, written in very broad terms, of variants from which the later filed claims seek to carve out a patentable portion. Each of the instantly filed claims represent variants with specific % identities and consecutive residues which encompass distinct molecules, of which there is no description or disclosure in the parent specification. The general recitation in the parent specification ('228) would not lead one of skill in the art to any particular species now claimed. The response at page 20, reasserts that the claimed subject matter need not be described in haec verba and that the parent specification ('228) discloses using two molecules: cellulose and carboxymethylcellulose (CMC), which provides support for the instantly claimed methods directed to modifying small molecules. This argument has been thoroughly reviewed but was found unpersuasive. As noted in the previous office action, the term "small molecule" not been defined in the instant specification to limited to CMC or cellulose. This recitation represents a very broad genus of molecules which includes for example, including any carbohydrate, lipid, peptide, nucleic acid, or organic or inorganic molecule, of which cellulose and CMC are not representative. The instantly filed claims are a broadening of the invention disclosed in the parent applications, and one of skill in the art would

not recognize from the disclosure of the parent specifications that applicants had invented a method of modifying *any* small molecule. Cellulose and CMC are structurally and functionally distinct from peptides, lipids, and nucleic acids, for example. They also represent distinct complex carbohydrates which are not representative of any carbohydrate, such as lactose, for example. For these reasons and the reasons made of record in the previous office action, the previous office actions' assessment of priority of the instantly pending claims is maintained. It is noted that newly added claims 134-138 are awarded a priority date of 6/22/2001 for the reasons made of record in the previous office action, section 5.

Claim Rejections - 35 USC § 112

Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 42-55, 88-96, 101, 103, 106, 107, 110-112, 115-133 and newly added claims 134-138 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are drawn generally to making variants of a polypeptide encoded by SEQ ID NO: 1 with endoglucanase enzymatic activity by either modifying SEQ ID NO: 1 or obtaining a nucleic acid already encoding a variant of SEQ ID NO: 1 with at least anywhere from 70-99% identity to SEQ ID NO: 1 or a variant of SEQ ID NO: 1 with at least 30, 40, or 75 consecutive residues with a sequence having anywhere from 70-99% identity to SEQ ID NO: 1, and possessing endoglucanase enzymatic activity, and modifying the variant, wherein the objective of all embodiments is to modify the nucleic acid by modifying one or more nucleotides to another nucleotide, deleting one or more nucleotides, or adding one or more nucleotides to obtain a variant encoding an enzyme with any endoglucanase activity. The claims are further drawn to using such a peptide to modify any small molecule. The specification does not define what is encompassed by the recitation of "small molecule" and therefore the claims broadly encompass the modification of any "small" molecule which includes any carbohydrate, lipid, peptide, nucleic acid, or organic or inorganic molecule by any 'variant' of SEQ ID NO: 2 with the requisite % identity and consecutive residues. The specification, however, does not teach how to make the broadly recited variants, nor which 'small' molecules would be predictably modified by such a broad scope of variants.

The amount of direction or guidance:

The specification provides inadequate guidance to allow the skilled artisan to determine, without undue experimentation, which of the myriad of possible deletion, substitution, or insertion mutations of SEQ ID NO: 1 would encode a polypeptide which would be likely to retain enzymatic activity. While the specification teaches how to generally make variants of proteins (see for example page 19, 3rd para; page 20, 2nd full para; pages 25-26; page 27 2nd and 3rd para; pages 33-36, page 42, pages 48-52), the use of computer programs to determine sequence homology (see pages 62-67) and generally how to screen for variants (see for example page 22; pages 25-26), the specification provides no guidance regarding the effects of substitution and/or insertion or deletion mutations on enzymes with carboxymethyl cellulase activity, or the ability to hydrolyze the beta 1,4 glycosidic bond in cellulose, the domain structure of the protein, the location of the active site or sites of interaction with cofactors or regulatory molecules, the molecular basis of the protein's activity, its secondary and tertiary structure, the importance of domains in maintaining activity, etc. Accordingly, the skilled artisan would not be able to determine which proteins encoded by nucleic acids with the required % identity or consecutive bases, or capability to hybridize under the disclosed hybridization conditions, would predictably retain endoglucanase activity, including for example, carboxymethyl cellulase activity. Further, the specification provides no guidance as to which 'small' molecules would be capable of modification by the broadly recited variants set forth in the claims.

Presence and absence of working examples:

The specification provides no working examples of making any variants of SEQ ID NO: 1 which encode an enzyme with endoglucanase enzymatic activity such as the ability to hydrolyze the beta 1,4, glycosidic bond in cellulose or with carboxymethyl cellulase activity, nor does the specification provide any working examples of modifying any small molecule with any such variants.

The state of the prior art and the predictability or unpredictability of the art:

The art specifically addresses the unpredictability of modifying endoglucanases by site directed mutagenesis to attain a molecule with any specific activity or ability to modify any cellulose substrate. For example, Pons (Pons et al; The J. of Biol. Chemistry; vol. 20, pages 13006-13012, 1997) teaches making mutants of 1,3 1,4 glucan glucanhydrolase from *B. licheniformis*, and teaches that some mutants, M58A notably, had surprising effects that were unpredictable from a simple structural analysis since the side chain of Met-58 does not interact with the substrate or with any essential catalytic residues in the 3-dimensional structure of the free enzyme (se page 13011, col. 2). Further, Pons specifically teaches that another remarkable mutant, N57A with increased thermostability, was obtained and that the effect of this mutation as well as the M58A mutation were unpredictable with current knowledge of protein structure/function relationships (see page 13011, col. 2, last para). Additionally, Zhang (Zhang and Wilson, Journal of Biotechnology, vol. 57, pages 101-113, 1997) teaches that surface residue mutants of endoglucanase E2 from *Thermomonospora fusca* had significant changes on the substrate specificity of the enzyme (see table 1, and page 109, col 1, first para). Zhang teaches

that 12 different surface residues were found in sugar binding sites and conserved in endoglucanases in family 6 and were mutated to non sugar binding residues. Zhang teaches that most of the mutants did not show major changes in activity, but that some do, the most striking of which was W16I which is from the active site (see page 111, col. 1, last full para). Thus Zhang illustrates that actual mutations must be made to determine the effect of a particular residue. Further, Zhang teaches that while a G87A mutation had a larger effect on activity that a G86A mutation, as predicted, it was also predicted that Cys mutations would increase activity, but did not (see page 112, col. 1). Thus Zhang also illustrates the unpredictability with regard to mutations in endoglucanases and the resulting effect on endoglucanase activity as well as the fact that the effect on substrate specificity is elucidated by actual mutagenesis, and not only by predictive analysis.

The art further teaches of the unpredictability of using structural homologies between proteins to predict function. Fetrow teaches (Fetrow et al., J. Mol. Biol., vol. 282, pp 703-711, 1998) that although function prediction by homology to previously characterized proteins is extremely successful and is fast, cheap and reliable, there are several problems that limit its potential utility, one of which is that sequence homology does not guarantee functional similarity (p 704, col. 1, 1st full paragraph). Fetrow teaches that "threading"(analysis using structure prediction tools) can identify topological cousins, that is, protein families such as the α/β barrels with similar structures, but dissimilar functions. Fetrow teaches using a three dimensional descriptor of the active site of a protein, termed "fuzzy functional form" (FFF) and argues that threading alone is not enough to provide the required information about function because it has been shown that pairs of proteins can have similar structures but unrelated functions (p. 706, col.

2, last para). Fetrow teaches that because such topological cousins exist, knowledge of the structure is not equivalent to identification of protein function. Skolnick (Skolnick and Fetrow, TIBTECH, January 2000, vol. 18, pp 34-39) teaches (p. 35, "Box 1") that a common protein characteristic that makes functional analysis based only on homology especially difficult is the tendency of proteins to be multifunctional. Skolnick teaches that for example, lactate dehydrogenase binds NAD, substrate, and zinc and performs a redox reaction and that each of these occurs at different functional sites that are in close proximity and the combination of all four sites creates the fully functional proteins. Skolnick also cites RecA which contains a DNA binding domain, a multimerization domain and additional sites that bind regulatory proteins. Skolnick also teaches that the serine threonine phosphatase superfamily is a prime example of the difficulties of using standard sequence analysis to recognize the multiple functions found in single proteins. Skolnick teaches that this large protein family is divided into a number of subfamilies, all of which contain an essential phosphatase active site. He teaches that subfamilies 1, 2A and 2b exhibit 40% or more sequence identity between them, however each of these subfamilies is apparently regulated differently by the cell and observation suggest that there are different functional sites at which regulation can occur. Skolnick teaches that because the sequence identity between subfamilies is so high, standard sequence similarity methods could easily misclassify new sequences as members of the wrong subfamily if the functional sites are not carefully considered. The art specifically teaches, that sequence alignment alone does not necessarily provide a predictable correlation between the structure and specific function of a protein.

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

It would require undue experimentation for one of skill in the art to practice the invention as broadly as it is claimed. The instant specification provides insufficient guidance to allow the skilled artisan to predict beforehand, the effects of particular deletion, substitution and/or insertion mutations of the claimed SEQ ID NOS. Given that the art specifically teaches of the unpredictability of making modifications in endoglucanases and obtaining a desired activity, teaches that actual modifications are needed to determine the effect of a specific residue on the activity and substrate specificity of endoglucanases, and teaches that sequence alignment alone does not necessarily provide a predictable correlation between the structure and specific function of a protein, the skilled artisan would have to perform extensive trial and error manipulations, the effect of each mutation being unpredictable on the activity and substrate specificity of the resulting protein variant, to determine which proteins would be predictably encoded by nucleic acids which possessed the recited % identity, contiguous fragments, or ability to hybridize to other nucleic acids under the recited conditions. While the specification generally teaches how to make variants of proteins and how to screen for activity, such is a teaching of how to find particular proteins which fall within the scope of the instantly pending claims, not how to make them. However, the requirements of 35 USC 112/first paragraph are that the specification be enabling for one of skill in the art to make and use the claimed invention. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example balanced only against the high

skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response as well as the declaration submitted under 37 C.F.R. by Dr. Jay Short have been thoroughly reviewed but were found unpersuasive for the reasons which follow. At page 22, last para –page 23 the response asserts that Pons supports the idea that it was routing and predictable to use mutagenesis techniques to make and identify active variant enzymes and that Pons demonstrates that variants could be predictably generated and routinely tested/screened for activity and stability without undue experimentation. This argument has been thoroughly reviewed but was found unpersuasive. While Pons teaches that scanning and random mutagenesis strategies are useful approaches to obtain proteins with improved properties, the method used by Pons was directed to specific changes in a small number of amino acids related to substrate binding. Even given this limited number of changes, Pons teaches that effects of the mutations made by Pons were unpredictable with current knowledge of protein structure/function relationships. Pons demonstrates that while mutagenesis techniques were used in 1997, the application of such to make a variant with a certain function was unpredictable.

At pages 23-24, the response asserts that the methods of Zhang are all subject to high throughput analysis and that while Zhang, like Pons, may teach that predictive analysis is not exactly accurate, it demonstrates that most non active site mutations did not show major changes in enzyme activity. This argument has been thoroughly reviewed but was found unpersuasive. Zhang teaches (at page 103, col. 1, end of first full para) that a region outside the active site is

suspected to be responsible for hydrolysis of insoluble cellulose but not for soluble substrates. Thus, Zhang supports the fact that non active site changes could affect activity. While Zhang teaches that mutants did not show major changes in activity, Zhang does teach that some do, the most striking of which was W16I which is from the active site (see page 111, col. 1, last full para). Thus Zhang illustrates that actual mutations must be made to determine the effect of a particular residue. Further, Zhang teaches that while a G87A mutation had a larger effect on activity that a G86A mutation, as predicted, it was also predicted that Cys mutations would increase activity, but did not (see page 112, col. 1). Thus Zhang also illustrates the unpredictability with regard to mutations in endoglucanases and the resulting effect on endoglucanase activity as well as the fact that the effect on substrate specificity is elucidated by actual mutagenesis, and not only by predictive analysis.

With regard to applicant's arguments regarding high throughput analysis and that both of the methods of Pons and Zhang could be used in high throughput analysis, as well as the response's arguments at page 27, which reiterates Dr. Short's declaration at page 1-2 of the declaration stating that method for making and screening endoglucanases were sufficiently comprehensive and routine at the time of the invention to predictably generate a genus of endoglucanase encoding enzymes without need of knowing or predicting beforehand which specific regions or structural elements of a sequence or structure affected it's activity, such arguments and the declaration have been thoroughly reviewed but were found unpersuasive. Both the teachings of Pons and Zhang are drawn to making a small number of changes in specific portions of the protein. Further, the assertions of Dr. Short support the fact that mutagenesis and screening were routinely used in the art at the time of the invention, however

the claims are not simply directed to methods of screening. The instantly pending claims encompass making an extremely large number of mutations anywhere in a sequence which is, for example, only 70% identical to SEQ ID NO: 1. Such % identity encompasses a sequence with 498 nucleotide changes in SEQ ID NO: 1. Were such changes made in independent codons, such variant could encompass a protein with 498 out of 552 amino acid residues changed as compared to the polypeptide of SEQ ID NO: 2. While the claims do encompass taking such a variant and modifying each base to make a sequence that is identical to SEQ ID NO: 1, the scope of the claims is much broader and encompasses making hundreds of thousands of variants. The instantly filed specification, however, does not demonstrate making any variants with endoglucanase enzymatic activity, nor does the specification provide any guidance as to making any specific variants. While the specification generally discloses methods of making variants, as well as envisioning making conservative and non conservative substitutions (regarding arguments made at pages 25-26 of response), such represents an invitation for the skilled artisan to experiment to determine enabled embodiments that would function within the scope of the claimed invention. This represent an invitation to "find" embodiments, it is not a teaching of how to make any specific variant with endoglucanase enzymatic activity. The skilled artisan would be required to perform an extensive amount of unpredictable trial and error analysis to find enabled embodiments. However, case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" In re Wright 990 F.2d 1557, 1561. In re Fisher, F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the

specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the unpredictability in the art. Furthermore, the Court in Genetech Inc. V Novo Nordisk 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

At page 24-25, the response asserts that the Fetrow and Skolnick references actually support the idea that, while sequence homologies between proteins cannot exactly predict what changes in enzyme function may be caused by a structural modification, sequence homology analysis does provide "powerful" guidance in identifying residues of active sites and other structural elements which may effect enzyme activity. This argument has been thoroughly reviewed but was found unpersuasive. Firstly, as acknowledged by the response, both Fetrow and Skolnick references support that sequence homologies between proteins cannot exactly predict what changes in enzyme function may be caused by a structural modification. The enablement requirement of 35 USC 112/first paragraph requires that the specification enable one of skill in the art how to make and use the invention commensurate in scope with the claims. In the instant case, the teachings of the specification, coupled with the knowledge available post filing (parent specification filed 1996) represents an invitation for the skilled artisan to perform unpredictable trial and error analysis to find enabled embodiments. The specification provides no teaching or guidance as to making any specific variants with any particular activity. The teachings of Skolnick or Fetrow do not make up for the deficiencies in the specification as neither reference provides any guidance on making any specific endoglucanase enzyme variants, or modifying any variant to obtain an endoglucanase. At page 24, the response asserts

"Additionally, it appears Fetrow considered the actual 'wet lab' screening for enzyme activity routine and predictable". Such argument has been thoroughly reviewed but was found unpersuasive as the examiner could not find a teaching in Fetrow regarding "routine and predictable" experimentation. Additionally, it should be noted that the instantly pending claims are directed to methods of making variants with endoglucanase enzymatic activity, not to methods of screening variants for activity.

At pages 26-28, the response cites Dr. Short's declaration. The response asserts that " if the artisan at the time of the invention elected to use elements of enzyme structure for guidance in designing and making variants (e.g., as to which amino acid residues can be substituted, deleted or inserted into a nucleic acid to obtain structural, and functional homologues of an enzyme), the skilled artisan could find such direction in the art at the time of the invention. For example, Dominguez (1996) "The crystal structure of a family 5 endoglucanase mutant in complexed and uncomplexed forms reveals an induced fit activation mechanism" J. Mol. Biol. 25745):1042-1051, describes the crystal structure of an endoglucanase; Ducros (1995) "Crystal structure of the catalytic domain of a bacterial cellulase belonging to family 5", Structure 3(9)2939-49, describes the crystal structure of the catalytic domain of an endoglucanase; Davies (1995) "Structures of oligosaccharide-bound forms of the endoglucanase V from *Humicola insolens* at 1.9 A resolution," Biochemistry 34(49):162 10-20, describes the crystal structures of an endoglucanase in various forms. Accordingly, one skilled in the art at the time of the invention using the teaching of the specification had many sources of direction to understand the structure of endoglucanases and have direction and guidance in determining which amino acid residues could be substituted, deleted or inserted into a nucleic acid to obtain structural and

functional variants of the exemplary endoglucanase of the invention". This argument as well as Dr. Short's declaration have been thoroughly reviewed but were found unpersuasive. Neither the response, nor the declaration provide guidance as to teachings with regard to any of the references and how they would teach one of skill in the art how to make endoglucanases commensurate in scope with the claims. Further, as noted above, the Court in Genetech Inc. v Novo Nordisk 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". None of the instantly cited references appear to teach how to make endoglucanases as required by the instantly pending claims. Such references, along with the very general teachings in the specification leave it up to the skilled artisan to use unpredictable trial and error analysis to find enabled embodiments.

At pages 28-29, the response asserts that experimentation is not considered undue, even if it is extensive, it if is routine or if the specification provides reasonable guidance regarding the direction of experimentation. The response further asserts (page 29) that "As declared by Dr. Short, the screening procedures used to make and identify nucleic acids and polypeptides of the invention, including high throughput screening assays, were all well known in the art at the time the application was filed. These procedures provided routine protocols for the skilled artisan that yielded predictably positive results.". This argument has been thoroughly reviewed but was found unpersuasive. The instantly filed claims are not directed to methods of screening for variants to determine which have endoglucanase activity, but to methods of making variants, as well as methods of modifying any small molecules with variants having endoglucanase activity. The specification only provides a general teaching of modifications which could be assayed for

activity, but does not teach any specific variants with enzymatic activity. As exemplified by the state of the art, making any specific variant with a particular activity is unpredictable, even with methods that are used in high throughput screening. While making mutants and screening for activity are methods that are used in the art, the experimentation required to obtain functional variants *from the sequences that are encompassed by the broad scope of the instantly pending claims* is replete with unpredictable trial and error analysis. For these reasons and the reasons made of record in the previous office action, the rejection is maintained.

Claim Rejections - 35 USC § 102

7. Claims 88, 89, 93, 95, 96, 101, 103, 106, 107, 110, 112, 115, 117-119, 124-133, and newly added claims 134-138 are rejected under 35 U.S.C. 102(b) as being anticipated by Lam (Lam et al; US Patent 6,074,867, 6/13/2000).

Lam teaches the sequence of the endoglucanase encoded by the sequence of SEQ ID NO: 1, as well as the protein of SEQ ID NO: 2 which are identical to the sequences of SEQ ID NO: 1 and SEQ ID NO: 2 recited in the instant specification. With regard to the claims directed to making variants, such claims encompass making variants of SEQ ID NO: 1. Lam inherently teaches making variants of a polypeptide encoded by SEQ ID NO: 1 in teaching non naturally occurring variants of the polypeptide encoded by SEQ ID NO: 1 (see col. 7, line 60- col. 9, line 22). With regard to the claims drawn to methods of modifying small molecules, Lam teaches that the polypeptide encoded by SEQ ID NO: 1 can be used for the degradation of cellulose for the hydrolysis o the beta 1,4 glycosidic bonds in CMC (col. 13, lines 24-29; col. 7, lines 22-32).

Response to Arguments

8. The response traverses the rejection on the grounds that the claims can properly claim benefit of priority to the parent application 08/651,572, filed May 22, 1996. This argument has been thoroughly reviewed but was found unpersuasive for the reasons made of record above. The response further states that the '867 patent is a divisional of the '572 application, the disclosures of which are the same and that the office has denied priority to the '572 application because the disclosure does not support the instantly pending claims, but has used the '867 patent's disclosure as prior art under 35 USC 102. The response maintains that the disclosure of the parent specification provides sufficient support under 112,first paragraph for the instantly pending claims, but if arguendo the office's allegation were true, then this same disclosure cannot be an anticipatory reference and that the 102(b) rejection should be withdrawn. This argument has been thoroughly reviewed but was found unpersuasive. The inquiry as to whether a claim is supported under 35 USC 112,first paragraph is an issue of scope. The broad scope of a claim may not be supported by a specific disclosure, however this broad scope can encompass embodiments recited in the specific disclosure. The instantly rejected claims are each drawn a subject matter that is broader in scope than was supported by the '572 application, however they encompass specific embodiments which do find support in the '572 application. For example, claim 93 encompasses obtaining a nucleic acid which comprises all residues of a sequence having at least 70% identity to SEQ ID NO: 1, which is anticipated by the '867 patent. Claims directed to at least 40 consecutive residues encompasses 50 residues. While the '572 application does not provide support for all the instantly filed claims representing variants with specific % identities and consecutive residues which encompass distinct molecules, of which there is no

description or disclosure in the parent specification, the scope of such claims is broad and encompasses embodiments recited in the '867 patent. While the general recitation in the parent specification ('572) would not lead one of skill in the art to any particular species now claimed, claims directed to methods of modifying small molecules encompass using the polypeptide encoded by SEQ ID NO: 1 to modify CMC or cellulose, which is anticipated by the '867 patent. The claims recite using a nucleic acid having at least a certain % identity to SEQ ID NO: 1, which encompasses using a sequence with 100% identity to SEQ ID NO: 1. This specific embodiment is supported by the parent application. Further, while the *broad genus* of any small molecule is not supported by the '572 application, cellulose and CMC are small molecules, which are supported by the parent application. For these reasons and the reasons already made of record in the previous office action, the rejection is maintained.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. No claims are allowable

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jehanne Sitton

Jehanne Sitton
Primary Examiner
Art Unit 1634

5/16/05